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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,297	01/24/2005	Matthew Baker	MER-137	9233

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,297	BAKER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,21,30,33 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,30,33 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 18 December 2007 has been entered. Claims 2-20, 22-29, 31, 32, 34, 35 were canceled. New claims 39-43 were added.

Applicant elected the species SEQ ID NO:4 (residues 131-163 of SEQ ID NO:1) and amino acid substitutions species Phe142Ala, Val144Thr and Tyr145Pro (20 July 2007). **As was stated in the previous Office Action (28 September 2008, page 2), the instant claims are examined to the degree that they reflect the elected invention and no other embodiments. Applicant is reminded that the Examiner is not obligated to extend the search and examination when the elected or subsequent species is rejected under *any* of 35 USC 101, 102, 103 or 112 1st, paragraph.**

Claims 1, 21, 30, 33, 36-43 are pending and under examination.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 21, 30, 33, 36-38 (and new claims 39-43) remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention. The basis for this rejection is set forth at pages 3-7 of the previous Office Action (28 September 2007).

Applicant argues that currently amended claims 1 and 21 and the claims that depend therefrom are directed to a finite genus of specific polypeptides, which comprise SEQ ID NO: 1 with at least one specified amino acid residue substitution. Applicant argues that the application provides guidance on how to determine the immunological properties of the polypeptides and discloses the biological activity associated with human erythropoietin (EPO). Applicant argues that the biological activity and amino acid residue sequence of EPO were well known in the art at the time the application was filed, as indicated by the references listed in the background section of the invention. Applicant argues that methods for assessing the level of immunogenicity of the polypeptides were also known before the filing date of the application. Applicant cites pages 1-4 of the specification. Applicant argues that the Federal Circuit has held that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides adequate guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed.Cir. 1988). Applicant argues that in the present case, the amount of experimentation meets both alternative criteria from *In re Wands*. Applicant argues that the required experimentation is routine in nature, the application provides precise guidance with respect to the direction of experimentation, since the amino acid residue sequences of the polypeptides are set forth in the claims, including all of the possible amino acid residue substitutions, and the methods for gauging immunogenicity are

described in the specification and were known in the art. Applicant argues that this is even more evident in the case of claims 36 and 37, which specify the measure of immunogenicity, and for claims 38-43, which are narrowly drawn to the elected species. Applicant contends that claim 38 is directed to a genus of only three polypeptides, each with a single amino acid residue substitution in SEQ ID NO:1, while claim 39 is directed to a genus of only seven polypeptides; three having a single substitution, one having three substitutions, and three having two substitutions in SEQ ID NO:1. Applicant states that clearly, any experimentation needed to practice claims 38 and 39 or their dependent claims 40-43 would neither be excessive nor undue.

Applicant's arguments have been fully considered but are not deemed persuasive. The specification fails to teach that the elected amino acid substitutions in EPO **1.** have the biological activity of human erythropoietin (EPO) **2.** are substantially non-immunogenic or less immunogenic than any non-modified molecule having the same biological activity in an individual when used *in vivo* and **3.** exhibited a stimulation index (SI) smaller than the parental non-modified molecule and smaller than 2.0 as recited in the instant claims. The specification states that mapping T cell epitopes in the EPO sequence using the T cell proliferation assay resulted in the identification of three immunogenic regions R1, R2 and R3 (page 26, lines 15-20). The specification states that multiple amino acid substitutions to achieve elimination of MHC class binding in EPO were made based on computational methods (page 28). The Examiner does not see where the elected EPO mutants were tested in a T cell stimulation/proliferation index to demonstrate a stimulation index smaller than 2.0 (or 1.8). The Examiner does

not see where the elected EPO mutants were administered *in vivo* to demonstrate that the mutants are substantially non-immunogenic or less immunogenic than any non-modified molecule having the same biological activity in an individual when used *in vivo*. The Examiner does not see where the elected EPO mutants have the biological activity of human erythropoietin. These limitations are recited in the instant claims and are purported to be the novelty of the instant invention. Thus, it is unclear how the instant claims can recite such limitations when the specification fails to teach these biological activities for the EPO mutants. The specification merely teaches the mapping of purported T cell epitopes (i.e. immunogenic regions) in the EPO sequence and then making predicted amino acid substitutions (to achieve elimination of MHC class binding) in EPO based on computational methods.

As was stated in the previous Office Action, Stickler et al. (reference of record) teach that epitope mapping of proteins is performed *in vitro* by measuring the proliferative responses of T cells presented with defined peptide molecules. Stickler et al. teach that several software programs have been made available that use the accumulated data from T cell mapping and HLA binding peptide information to predict HLA binding epitopes in proteins of interest. **Stickler et al. state that despite their power and accuracy, they only predict HLA binding, and thus the suggested epitopes for a given protein must be validated using *in vitro* T cell stimulatory assays (page 654, last paragraph-page 655).** For example, Stickler et al. teach the region around the E05/06 peptide as the major T cell epitope in a bacterial subtilisin protein based on the level of stimulation indices. The epitope in bacterial subtilisin was

mutated and then re-tested using *in vitro* T cell stimulatory assay. Stickler et al. teach that some mutation changes in the sequence appear to have greatly interfered with the peptide's ability to induce a proliferative response. However, changing certain residues in the sequence caused an up-regulation in the *in vitro* T cell stimulatory assay (Figure 3). Stickler et al. teach that this phenomenon is not uncommon and points to the potential for changes in immunogenic when manipulating protein molecules to change their functions. Stickler et al. teach that predicted results must always be validated because HLA binding is necessary but not sufficient to define a fully functionally T cell epitope. A functional epitope includes residues that can be recognized by a T cell receptor of the correct specificity and with an appropriate binding affinity (page 658). Wells and Ngo et al. (references of record) were submitted in the previous Office Action to show that certain positions in the sequence are critical to the protein's structure/function relationship. An active or binding site must assume the proper three-dimensional configuration to be active. Conformation is dependent upon surrounding residues and therefore substitution of non-essential residues can often destroy activity. The substitution of non-essential residues can often make the protein differ substantially.

Applicant argues that currently amended claims 1 and 21 and the claims that depend therefrom are directed to a finite genus of specific polypeptides, which comprise SEQ ID NO: 1 with at least one specified amino acid residue substitution. Applicant's arguments are not found persuasive. Applicant is reminded that the instant claims are examined to the degree that they reflect the elected invention and no other

embodiments. However, even if the instant claims were being examined fully on the merits, claims 1 and 21 do not place any limitation on the number of substitutions which can be made in EPO and still have the claimed function. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed protein. As plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Applicant contends that claim 38 is directed to a genus of only three polypeptides, each with a single amino acid residue substitution in SEQ ID NO:1, while claim 39 is directed to a genus of only seven polypeptides; three having a single substitution, one having three substitutions, and three having two substitutions in SEQ ID NO:1. Applicant argues that any experimentation needed to practice claims 38 and 39 or their dependent claims 40-43 would neither be excessive nor undue.

Applicant's argument is not found persuasive. Based on the art of record, one of ordinary skill in the art would have reason to doubt that the functional limitations would be possessed by any one of the elected EPO mutants, and thus any combination of the elected EPO mutants would not be enabled. As was stated above, an *in vitro* T-cell proliferation assay was used to map T cell epitopes and identify three immunogenic regions (R1-R3) with the EPO molecule. A computational method was then employed to

make preferred substitutions in each of the epitope regions R1-R3 of EPO. The specification does not go further into characterizing the mutant R1-R3 regions to discern immunogenicity or biological activity. The specification does not teach reduced binding of the elected mutant EPO peptides to MHC class II molecules. The specification does not teach that the elected mutant EPO molecules have a stimulation index (SI) smaller than the parental non-modified molecule and smaller than 2.0 (i.e. less immunogenic) using a T cell proliferation assay. The specification does not teach that the elected mutant EPO molecules have the biological activity of human erythropoietin (EPO). **The specification fails to teach the claimed activity for the elected EPO mutant species.** The specification merely teaches mutated EPO molecules which are purported to have the claimed activity.

The Examiner does not doubt that *epitope predictions* can be made based on various computer programs, software, etc. However, it cannot be said that the predicted T-cell epitopes are true T-cell epitopes *in vivo* or that introduced substitution changes will not introduce new immunogenic sites in the protein or alter the biological activity without testing the protein. The art of record teaches that epitope predictions based on computer programs or software alone, are unpredictable. The art of record also teaches that substitution of non-essential residues can often make the protein differ substantially. The issues of the instant application with respect to *In re Wands* are the level of predictability in the art and that lack of guidance resulting in undue experimentation. A considerable amount of time is permissible if the invention is merely routine or if the skilled artisan is given sufficient direction or guidance. The amount of

guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention to be enabling. **In the instant case, the references of record teach that the art is unpredictable (computational epitope predictions, substitutions of non-essential residues) and the specification fails to teach those elected EPO mutants that would have the claimed activity.** Thus, the required experimentation is not routine in nature because the art is unpredictable and the specification fails to provide guidance with respect to the direction of experimentation. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
3/26/08